(estimated spectrophotometrically). In a similar manner, N^4-benzoylcytidine and N^2-benzoylguanosine were obtained in 99% and 98% yields, respectively.

Deblocking of the Fully Protected Hexanucleotide UUGACA (20). The hexamer **20** (41.8 mg, 10 μmol) was treated with $ZnCl_2$ (244 mg, 1.8 mmol) in aqueous pyridine (90%, 15 mL) at room temperature for 30 h. Then water (5 mL) and Dowex 50W-X2 (pyridinium form) were added with stirring. The resin was removed by filtration and washed with aqueous pyridine (50%). The filtrate and washings were collected and then evaporated to dryness. The residue was dissolved in methanolic ammonia (10 mL), and the mixture was kept at 23 °C for 36 h. The solution was concentrated, and the residue was treated with triphenylmethyl fluoroborate (44 mg, 200 μmol) in CH_3CN–H_2O (4:1 v/v, 2 mL) at room temperature for 3 h. Pyridine was added to the reaction mixture, and the solution was evaporated in vacuo. The deblocked product **21** was isolated by ion-exchange chromatography on a column (1.0 × 70 cm) of DEAE cellulose. The main part of the peak in Figure 1 (303 A_{254}) was purified and isolated by HPLC (Figure 2) in 70% yield. U-U-G-A-C-A (**21**) was characterized by base composition analysis by anion-exchange HPLC after complete digestion with nuclease P1. The ratio of pU/pG/pC/pA was 1.00:0.91:1.14:2.19: R_f 0.26 (solvent A); paper electrophoresis 0.83 (to Cp); UV (H_2O, pH 7.0) λ_{max} 258 nm, λ_{min} 234.

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Registry No. 1, 42822-78-6; **2**, 80015-57-2; **3**, 85193-75-5; **4b**, 3676-72-0; **5a**, 80015-55-0; **5a**·HCl, 87985-90-8; **5b**, 80015-56-1; **7a**, 87985-91-9; **7b**, 87985-92-0; **8**, 80015-59-4; **9a**, 85193-78-8; **9b**, 80015-61-8; **9c**, 87985-93-1; **10a**, 85193-79-9; **10b**, 80015-63-0; **11**, 87985-94-2; **12**, 87985-95-3; **13**, 88015-19-4; **14a**, 87999-43-7; **14b**, 80015-66-3; **15a**, 87985-97-5; **15b**, 80015-68-5; **16a**, 87985-96-4; **17a**, 87999-40-4; **17b**, 88015-18-3; **18**, 87999-41-5; **19**, 80015-70-9; **20**, 88083-16-3; **21**, 87999-42-6; 4-methoxybenzyl bromide, 2746-25-0; cytidine, 65-46-3.

Convergent and Efficient Synthesis of Spiro[benzofuran-3(2*H*),4′-piperidines]

Saul H. Rosenberg and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California 94720

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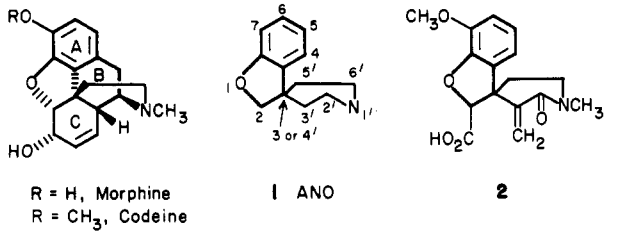
A synthesis is presented of spiro[7-methoxybenzofuran-3(2*H*),4′-piperidines], tricyclic analogues containing the A, N, and O rings of codeine. Two successive 1,4-additions into a pyridine residue, an intermolecular aryllithium addition followed by an intramolecular ester enolate ring closure, establish the spiro[benzofuran–dihydropyridine] system. Reduction and finally α-methylene lactam rearrangment provide the necessary functionalization for further elaboration and C-ring closure.

A broad class of biologically potent compounds are the 4,4-disubstituted piperidines. Although certain members are well documented for analgesic activity,[1] it is only recently that the wide-ranging pharmacological properties and commercial value of these compounds have been demonstrated.[2] An important group of analgesics within the disubstituted piperidines are the spiro[benzofuran-3-(2*H*),4′-piperidines] **1** containing three rings (ANO) of the pentacyclic morphine skeleton. Recently this fragment has been proven a viable intermediate for further elaboration into the codeine system.[3]

Early syntheses of the spiro[benzofuran-3(2*H*),4′-piperidines] have employed a geminal alkylation by a bis(2-haloethyl)amine to produce a structure containing a fully saturated, unsubstituted nitrogen ring. Functionalization of both the C-2 side chain and of the nitrogen ring has been achieved with a sequence in which the C-4′ position is quaternized through an α-chloro ortho ester rearrangement.[3] Recently a route involving an intramolecular addition to a pyridinium species has appeared.[4] The last method provides functionalization of the piperidine ring in the form of unsaturation but does not incorporate the C-7 oxygen substituent necessary for the codeine functional group pattern.

Enolate additions to 3-carbonylpyridinium salts have been employed in a variety of natural product preparations.[5] We now present a route to the synthesis of **2**, which



R = H, Morphine
R = CH_3, Codeine

1 ANO

2

has been elaborated to an octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline,[3] by employing this methodology along with the well-known α-methylene lactam rearrangement.[6]

(1) Schaumann, O. *Arch. Pathol. Exp. Chem.* **1949**, *196*, 109.
(2) Analogesics, narcotic antagonists: (a) Ciganek, E. U.S. Patent 4 243 668, 1981; *Chem. Abstr.* **1980**, *95*, 80924. (b) Dammortz, W.; Reimann, E. *Arch Pharm.* **1982**, *315*, 27. (c) Zimmerman, D. M.; Nickander, R.; Horng, J. S.; Wong, D. T. *Nature (London)* **1978**, *275*, 332. (d) Ong, H. H.; Profitt, J. A.; Spaulding, T. C.; Wilker, J. C. *J. Med. Chem.* **1979**, *22*, 834. Vasodilators: (e) Goldmann, S. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 779. (f) Goldmann, S.; Bossert, F.; Kazda, S.; Vater, W. Eur. Pat. Appl. EP 42 566, 1981; *Chem. Abstr.* **1981**, *96*, 162547. Anticonvulsants: (g) Ong, H. H.; Profitt, J. A. U.S. Patent 4 209 625, 1980; *Chem. Abstr.* **1980**, *93*, 204474. (h) Ong, H. H.; Profitt, J. A. U.S. Patent 4 198 418, 1980; *Chem. Abstr.* **1980**, *93*, 71576.
(3) Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 5064 and references cited therein.
(4) (a) Weller, D. D.; Luellen, G. R. *Tetrahedron Lett.* **1981**, *22*, 4381. (b) Weller, D. D.; Weller, D. L. *Tetrahedron Lett.* **1982**, *23*, 5239.
(5) (a) Wanner, M. J.; Koomen, G. J.; Pandit, U. K. *Heterocycles* **1981**, *15*, 377. (b) Wenkert, E.; St. Pyrek, J.; Uesato, S.; Vankar, Y. D. *J. Am. Chem. Soc.* **1982**, *104*, 2244. (c) Wenkert, E.; Chang, C. J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *Ibid.* **1976**, *98*, 3645.

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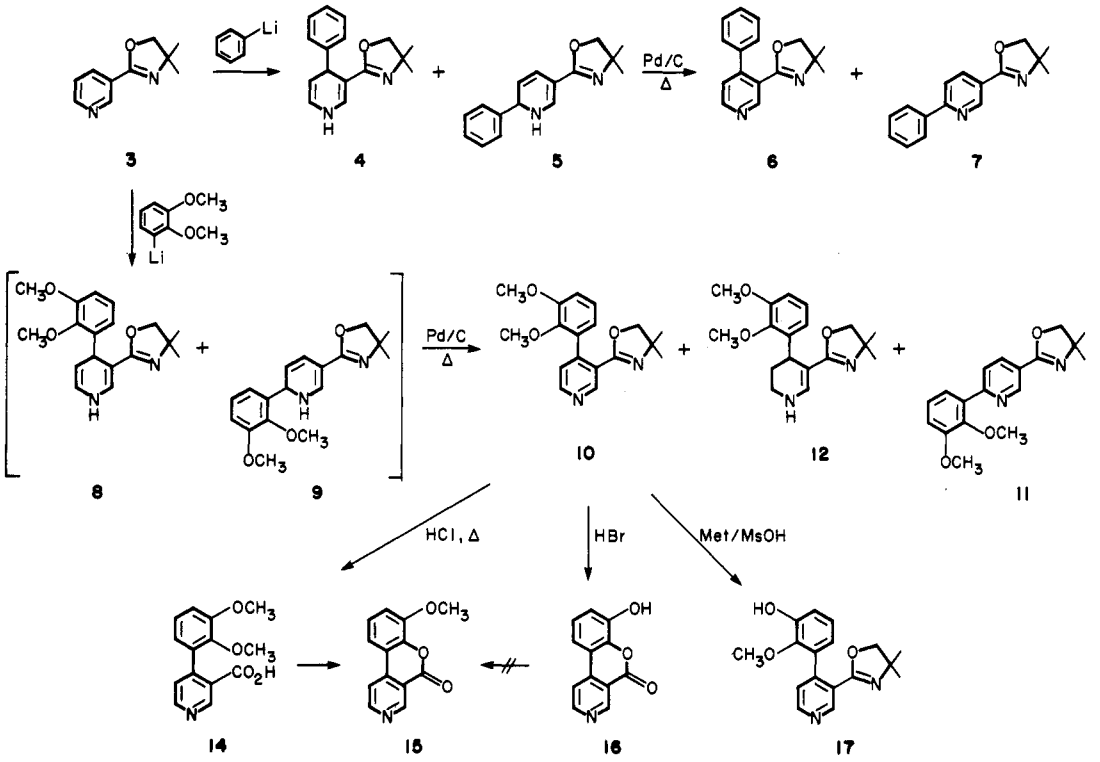
Scheme I. Aryllithium Reactions of (3-Pyridyl)oxazoline 3



Potentially a variety of C-2 side chains and nitrogen ring substitution patterns could be incorporated. Known methods for B-ring closure[7] could provide the entire pentacyclic codeine structure.

Results and Discussion

Lactone Preparation. Our synthetic scheme required 4-arylpyridine lactone **15** as the key intermediate. Although a variety of such compounds is known,[8] none have been prepared which are unsubstituted in the 2-, 5-, and 6-positions of the pyridine ring. The only 4-arylnicotinates so structured bear only an unsubstituted phenyl ring. These have been prepared by selective decarboxylation of the 4-phenyl 2,5-dicarboxylic acid (prepared from 2,5-dimethyl-4-piperidinone),[9] by free-radical substitution of 3-cyanopyridine,[10] and by addition of phenyllithium to a 3-oxazolinylpyridine followed by oxidation of the resulting dihydropyridine.[11] This last procedure is the only one of synthetic utility.

Although phenyllithium has been reported to add to the 4-position of (3-pyridyl)oxazoline **3** (Scheme I) in ether at room temperature[11a] or in THF at −78 °C,[11b] we have found that the course of the reaction is both temperature and solvent dependent (Table I). At higher temperatures and in ether a second phenyldihydropyridine, **5**, was formed in significant amounts. Although analysis was difficult at this stage, oxidation to phenylpyridine **7** confirmed that addition to the 6-position had occurred.

Extension of this reaction to the 2,3-dialkoxyphenyl series was not immediately straightforward. 2,3-Dimethoxyphenyllithium[12] is sparingly soluble in both THF and ether, resulting in a minimum reaction temperature of −50 °C in THF (Table I). These conditions led to a 2/1 mixture of addition at C-6 and C-4, **9** and **8**, respectively.[16] Apparently steric interactions between the *o*-methoxy group and the oxazoline disfavor addition to the 4-position. More polar solvents such as glyme and an HMPA/THF mixture were decomposed by the lithium reagent. Addition of TMEDA had no effect. The Grignard reagent (from 1-bromo-2,3-dimethoxybenzene[13]) proved unreactive.

Table I. Isomer Distributions from the Addition of Aryllithiums to (3-Pyridyl)oxazoline 3

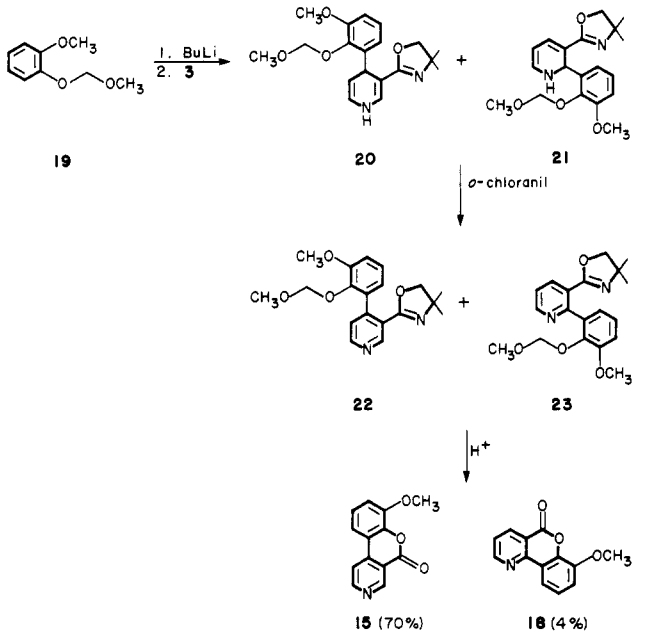
aryllithium	solvent	reaction temp, °C	reaction time, h	4-addition/6-addition ratio[a]
phenyllithium	THF	20	1	5 (4/5)
	ether	20	1	0.5
	THF	−78	0.75	>10
	ether	−78	1	6
2,3-dimethoxy-phenyllithium	ether	−23	4	6 (9/8)
	THF	−23	2	6
	THF	−45	2	2
	THF	−78	4	*b*

[a] By proton NMR. Crude yields were all in the range 90–100%. [b] No reaction.

Treatment of the dihydropyridine mixture of **8** and **9** with *o*-chloranil in toluene,[11b] DDQ in benzene,[11a] $KMnO_4$ in acetone,[11a] and iodine in ethanol[14] all produced inseparable mixtures although proton NMR analysis suggested that the 4-substituted (2,3-dimethoxyphenyl)pyridine **10** was present. Simply heating the dihydropyridine mixture with palladium on carbon in toluene gave pyridines **10** (10%) and **11** (40%). Tetrahydropyridine **12** was also recovered (10%), indicating that dihydropyridine **8** was

(6) Lee, D. L.; Morrow, C. J.; Rapoport, H. *J. Org. Chem.* **1974**, *39*, 893.
(7) Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 1324.
(8) Darbarwar, M.; Sundaramurthy, V. *Synthesis* **1982**, *337*.
(9) Prostakov, N. S.; Mikheeva, N. S. *Med. Promst. SSSR* **1960**, *14*, 11; *Chem. Abstr.* **1960**, *54*, 22637.
(10) Court, J.; Vidal, S.; Bonnier, J. M. *Bull. Soc. Chim. Fr.* **1972**, *3107*.
(11) (a) Hauck, A. E.; Giam, C. S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2070. (b) Meyers, A. I.; Gabel, R. A. *J. Org. Chem.* **1982**, *47*, 2633.
(12) Gilman, H.; Swiss, J.; Cheney, L. C. *J. Am. Chem. Soc.* **1940**, *62*, 1963.
(13) Stevens, R. V.; Bissachi, G. S. *J. Org. Chem.* **1982**, *47*, 2396.
(14) Weller, D. D.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 6650.

Scheme II. Direct Synthesis of Lactone 15 from Oxazoline 3



disproportionating rather than solely dehydrogenating under the above conditions.

If (dimethoxyphenyl)pyridine **10** was to be a viable intermediate, then a method for cleavage of the *o*-methyl ether was necessary. One obvious route to lactone **15** was to cleave both ethers as well as the oxazoline to give phenolic lactone **16** which could then be remethylated at the meta hydroxyl. The first transformation was readily accomplished with 48% HBr; however, the extreme insolubility of **16** made the alkylation only slightly successful. Other cleavage conditions, such as methionine and methanesulfonic acid,[3] showed only limited selectivity, producing a 2/1 mixture of **17**, in which the *m*-methyl ether had been cleaved preferentially, and **15**. Refluxing **10** in 6 M HCl did produce **15**; however, **16** was a major byproduct. Maximum yields were obtained by heating **10** in 6 M HCl for a short period, collecting **15** and recycling **14**. In this manner the amount of **16** was minimized, and **15** was produced in 60% yield, representing an overall yield of 6% from nicotinate derivative **3**. These transformations are summarized in Scheme I.

Although encouraging, the above results were far from satisfactory. What we required was an aryllithium reagent bearing an ortho substituent which would direct ortho metalation and which could be selectively removed. Furthermore, this group either should be less sterically demanding than a methyl group so that interactions with the oxazoline of **3** would be minimized or should be able to complex with the oxazole so that the reagent is directed into the 4-position. It was clear that the methoxymethyl group would satisfy the first two conditions. We believed that this group was also capable of coordinating with the imine of the oxazoline at least to the extent that steric effects would be cancelled.

Guaiacol was converted to its methoxymethyl ether **19** by treatment with sodium methoxide followed by chloromethyl methyl ether in THF at −23 °C (Scheme II). Higher termperatures or less polar solvents led to appreciable amounts of C-alkylation. Lithiation of **19** occurs selectively at the position ortho to the methoxymethyl group[15] to provide a THF-soluble reagent. In the reaction with **3**, a mixture consisting predominantly of one dihydropyridine was formed. Palladium-mediated dehydrogenation again resulted in disproportionation. Chloranil oxidation, however, proceeded cleanly to a mixture of 4-arylpyridine **22** and the 2-aryl isomer **23**. Treatment with mild acid produced lactones **15** (70% yield from **19**) and **18** (4%). No products resulting from addition at the 6-position were observed. Although all intermediates can be isolated and purified, only a final chromatography of **15** is necessary, and maximum yields are realized when intermediate isolations are avoided. Thus **15** is prepared in 56% from guaiacol with purification only of **19** and **15** (Scheme II).

Table II. Effect of Ester on Transesterification During Quaternization and Ring Closure of Nicotinate 24

substrate	yield from 15,[a] %	R	R′	26/27 ratio[b]
24a	85	Me	*t*-Bu	1
24b	87	Et	*t*-Bu	2
24c	79	*i*-Pr	*t*-Bu	*c*
24d	67	*i*-Bu	*t*-Bu	5
24e	93	Me	Et_3C	10
24f	96	Et	Et_3C	>20

[a] After MPLC. [b] As determined by HPLC (ether/isooctane mixtures) and ^1H NMR. [c] Use of isopropoxide resulted in decomposition of **24**.

Lactone Opening and Oxide Ring Closing. Lactone opening was accomplished by treating **15** with potassium *tert*-butoxide followed by methyl bromoacetate to provide 4-arylnicotinate **24a** (Scheme III). Treatment with lithium tetramethylpiperidide did not effect ring closure in contrast to when the pyridine ring is activated by esters in both the 3- and 5-positions.[2e] Quaternization with iodomethane followed by treatment with a variety of bases under aprotic conditions (LDA, LiTMP, KH, and *t*-BuOK in THF and DMF) resulted in extensive reaction to unrecognizable products. Ring closure could be effected under protic (methanol/methoxide) conditions; however, transesterification of the nicotinate ester was competitive. A tertiary ester had been chosen for this position so that it could be selectively hydrolyzed prior to the α-methylene lactam rearrangement. With this constraint, a variety of ester combinations were examined (Table II). Surprisingly, the *tert*-butyl group did not prevent transesterification which was effectively suppressed by using the bulkier 3-ethyl-3-pentyl (triethylcarbinyl) ester.

Ring closure of **24f** provided spirobenzofuran **26f** as a 10/1 mixture[17] of diastereomers. The major isomer was expected to have the stereochemistry in which the esters were on opposite sides of the plane of the aromatic ring (α isomer). This was confirmed by the upfield shift of the 2-proton, caused by its proximity to the triethylcarbinyl ester, when compared to the shift of this proton in the β isomer. Diastereomer separation, however, is unnecessary, and purification at the dihydropyridine stage resulted in large losses. Instead, hydrogenation and then sodium cyanoborohydride reduction[18] followed by a simple acid–base extractive isolation provided piperidine diester **29** in 75% yield from **24f** (Scheme III).

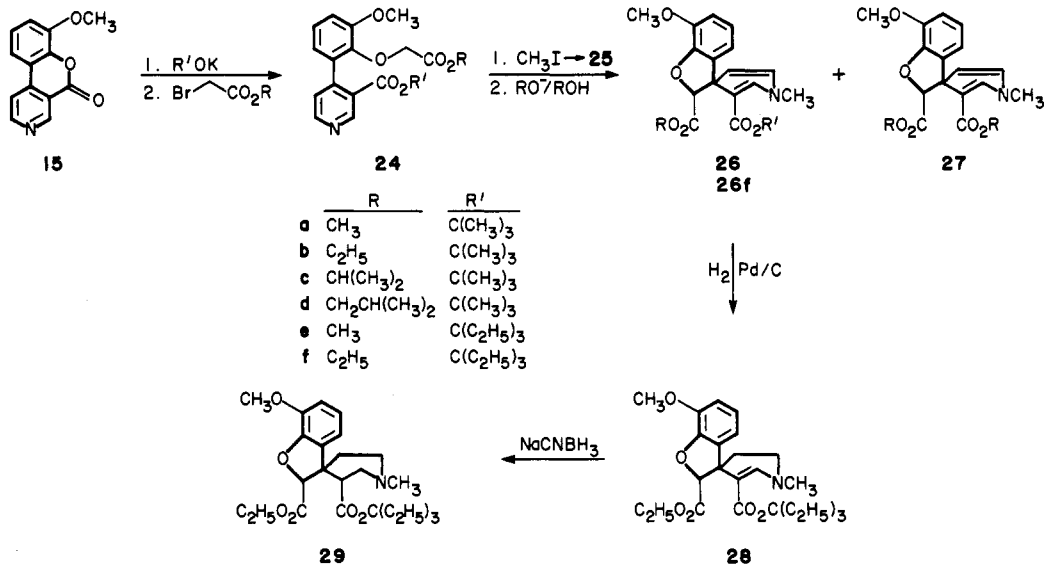
(15) Narasimhan, N. S.; Mali, R. S.; Burve, M. S. *Synthesis* **1979**, 906.

(16) A small amount of **18** was isolated at a later stage, indicating that addition to the 2-position was also occurring. The ratio of **18** to **15** was 1/20.

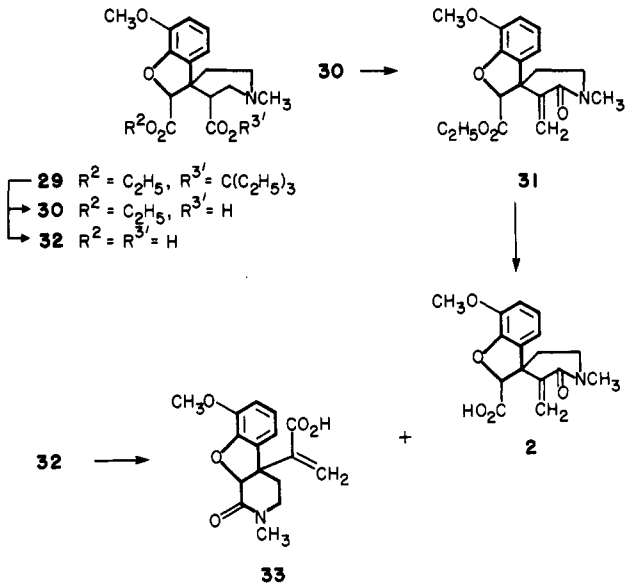
(17) When sodium ethoxide is replaced by lithium ethoxide, the ratio of α to β becomes 3/1. This is to be avoided since the cyanoborohydride reduction of the β isomer is quite sluggish.

(18) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

Scheme III. Lactone Opening and Oxide Ring Closure Sequence



Scheme IV. Rearrangement of Diester 29 to Methylene Lactam 2



Ester Hydrolyses and α-Methylene Lactam Rearrangement. Acid hydrolysis of diester **29** yielded ester acid **30**. Treatment with acetic anhydride at reflux effected rearrangement to afford methylene lactam **31** in 62% yield after chromatography (Scheme IV). Mild alkaline hydrolysis provided a quantitative yield of **2** identical in all respects with an authentic sample.[3] Thus with only four intermediate purifications **2** is prepared in 12 transformations from guaiacol in an overal yield of 25%. Unless **2** is to be used immediately, the final hydrolysis should be avoided and the product stored as **31**.

Conceptually **2** could be prepared directly through the α-methylene lactam rearrangment of diacid **32**, a procedure that would, of course, obviate the requirement for differentiated esters. The possibility existed, however, that once the piperidine ring had been opened, the resulting secondary amine could close upon either carboxyl to form lactam acids **2** and/or **33**. Ester acid **30** was hydrolyzed to diacid **32** which was subjected to the rearrangement conditions. The resulting product was immediately esterified to a 1/7 mixture of two lactam esters, **31** and a new compound. That this new product was simply the other (β) diastereomer of **31** was confirmed by an alkaline equilibration of **31** which gave the α and β diastereomers in a ratio of 1/17. Thus **2** can be prepared by both sequences, and either diastereomer can be made to predominate simply by changing the substrate in the α-methylene lactam rearrangement.

Experimental Section

General Methods. Tetrahydrofuran (THF) and toluene were distilled from sodium/benzophenone. Dimethylformamide (DMF) was stirred over calcium hydride (24 h), decanted onto and stirred with barium oxide (24 h), and finally decanted onto freshly activated neutral alumina and distilled at reduced (12 mm) pressure.[19] Methanol and ethanol were distilled from magnesium. 3-Ethyl-3-pentanol was distilled from calcium hydride. Acetic anhydride was fractionally distilled (2×) from P_2O_5. Methyl iodide was percolated through freshly activated basic alumina, and butyllithium was analyzed by titration.[20]

Boiling points and melting points (Pyrex capillary) are uncorrected. ^1H NMR spectra were determined on Varian EM-390 (90 MHz) or Berkely UCB 250 (250.80 MHz) spectrometers. ^{13}C NMR spectra were measured at 63.07 MHz with the UCB-250. Unless otherwise noted ^{13}C NMR and ^1H NMR spectra were recorded in $CDCl_3$, and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. UV spectra were determined in ethanol with a Perkin-Elmer 522A spectrophotometer. Low-resolution mass spectra were obtained with an Atlas MS 12 mass spectrometer. High-resolution (exact mass) mass spectra were obtained with a Du Pont 21-110 spectrometer. Elemental analyses were performed by the Analytical Laboratory, College of Chemistry, University of California.

Preparative medium-pressure liquid chromatography (MPLC) was done by using a Milton Roy minipump and a Beckman 153 UV detector set at 280 nm with Ace Michel-Miller glass columns and 40–60-mesh silica gel 60 (E. M. Reagents). Column chromatography (gravity) was performed with 63–200-mesh silica gel 60 (E. M. Reagents).

Unless otherwise noted, reactions were conducted under an argon atmosphere with magnetic stirring at room temperature. Final product solutions were dried over Na_2SO_4 and evaporated at reduced pressure with a Berkeley rotary evaporator.

3-(4,4-Dimethyl-2-oxazolinyl)-4-(2,3-dimethoxyphenyl)-pyridine (10) and 2-(2,3-Dimethoxyphenyl)-5-(4,4-dimethyl-2-oxazolinyl)pyridine (11). *n*-Butyllithium (14.0 mL, 22.4 mmol, 1.6 M in hexane) was added to veratrole (2.70 mL, 21.2 mol) in THF (150 mL) at 0 °C. After being stirred for 4 h, the suspension was cooled to −45 °C, **3**[11] (3.128 g, 17.7 mmol) in

(19) Thomas, A. B.; Rochow, E. G. *J. Am. Chem. Soc.* **1957**, *79*, 1843.
(20) Gilman, H.; Haubein, A. H. *J. Am. Chem. Soc.* **1944**, *66*, 1515.

THF (15 mL) was added over 1 h, and then the mixture was stirred for 1 h, warmed to 0 °C, stirred for 2 h, and quenched with saturated ammonium chloride solution (15 mL). The mixture was concentrated and diluted with ether which was then washed with water, dried, and evaporated to leave an oily yellow solid. A toluene (100 mL) suspension of this residue of crude dihydropyridines and 10% Pd/carbon (0.204 g) was refluxed for 6 h, filtered, and extracted into 1 M HCl which was made alkaline with potassium carbonate and extracted with chloroform. Evaporation of the solvent followed by chromatography (MPLC, 1% methanol, 0.05% TEA in chloroform) afforded 2.306 g (42%) of **11** and 0.565 g (10%) of **10**.

11: mp 61–63 °C; bp 140–150 °C (0.1 mm); ^{1}H NMR δ 8.75 (dd, 1 H, J = 4.8, 1.8 Hz), 8.18 (dd, 1 H, J = 7.8, 1.8 Hz), 7.32 (dd, 1 H, J = 4.8, 7.8 Hz), 7.10 (m, 2 H), 6.97 (dd, 1 H, J = 7.2, 2.6 Hz), 3.89 (s, 3 H), 3.88 (s, 2 H), 3.50 (s, 3 H), 1.27 (s, 6 H); ^{13}C NMR δ 162.4, 155.7, 152.4, 150.7, 137.7, 135.1, 125.4, 123.9, 122.4, 121.7, 113.1, 79.8, 67.5, 60.9, 56.2, 28.1; UV λ_{max} 250 nm (ϵ 9550). Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.2; H, 6.5; N, 9.0. Found: C, 69.3; H, 6.5; N, 8.9.

10: bp 140–150 °C (0.1 mm); ^{1}H NMR δ 9.03 (d, 1 H, J = 0.6 Hz), 8.67 (d, 1 H, J = 5.1 Hz), 7.31 (dd, 1 H, J = 0.6, 5.1 Hz), 7.10 (dd, 1 H, J = 8.2, 7.6 Hz), 6.97 (dd, 1 H, J = 8.2, 1.6 Hz), 6.84 (dd, 1 H, J = 7.6, 1.6 Hz), 3.91 (s, 3 H), 3.84 (s, 2 H), 3.54 (s, 3 H), 1.28 (s, 6 H); ^{13}C NMR δ 161.4, 152.7, 150.7, 150.4, 146.3, 145.9, 133.0, 125.2, 124.6, 123.8, 121.6, 112.8, 79.5, 67.6, 60.6, 56.0, 28.0; UV λ_{max} 255 nm (ϵ 8910). Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.2; H, 6.5; N, 9.0. Found: C, 69.1; H, 6.4; N, 8.9.

Further elution (96/3/1, ethyl acetate/2-propanol/TEA) and distillation afforded 0.590 g (11%) of a colorless oil to which structure **12** was assigned on the basis of its NMR spectrum: bp 150 °C (0.1 mm); ^{1}H NMR δ 7.44 (s, 1 H), 6.74 (m, 3 H), 4.33 (m, 1 H), 3.93 (s, 3 H), 3.83 (s, 3 H), 3.73 (s, 1 H), 3.70 (s, 1 H), 3.00 (m, 2 H), 1.83 (m, 2 H), 1.18 (s, 3 H), 1.08 (s, 3 H).

2-Phenyl-5-(4,4-dimethyl-3-oxazolinyl)pyridine (7) was prepared by the above procedure and was chromatographically separated (gravity column, 50/50 chloroform/ethyl acetate) from the more polar 4 isomer:[11] ^{1}H NMR δ 8.74 (dd, 1 H, J = 1.8, 4.8 Hz), 8.03 (dd, 1 H, J = 1.8, 7.8 Hz), 7.63 (m, 2 H), 7.40 (m, 3 H), 7.23 (dd, 1 H, J = 4.8, 7.8 Hz), 3.88 (s, 2 H), 1.33 (s, 6 H); ^{13}C NMR δ 162.8, 158.3, 150.9, 140.0, 138.5, 128.8, 128.6, 128.1, 124.0, 121.6, 79.8, 67.9, 28.0; UV λ_{max} 245 (ϵ 11 200); mass spectrum, m/z (relative intensity) 251 (100), 179 (10), 181 (6), 166 (10); exact mass calcd for $C_{16}H_{15}N_2O$ m/z 251.1185 (M − 1), found 251.1186 (M − 1).

7-Hydroxy[1]benzopyrano[3,4-*c*]pyridin-5(2*H*)-one (16). A solution of **10** (93 mg, 0.3 mmol) in 48% HBr (5 mL) was heated at 85 °C for 48 h. The solvent was evaporated, and the residue was taken up in 30 mL of a pH 6 phosphate buffer. Filtration gave a solid which was sublimed at 170 °C (0.05 mm) to afford 22 mg (44%) of **16**. Continuous extraction of the filtrate with chloroform (24 h) provided an additional 8.5 mg (13%) of product: mp >280 °C; ^{1}H NMr (Me_2SO-d_6) δ 9.37 (s, 1 H), 8.94 (d, 1 H, J = 6 Hz), 8.23 (d, 1 H, J = 6 Hz), 7.77 (dd, 1 H, J = 2, 7 Hz), 7.20 (m, 2 H); mass spectrum, m/z (relative intensity) 213 (100), 198 (23), 184 (72), 156 (52); exact mass calcd for $C_{12}H_7NO_3$ m/z 213.0426, found m/z 213.0417. Anal. Calcd for $C_{12}H_7NO_3 \cdot {}^1/_4H_2O$: C, 66.2; H, 3.5; N, 6.4. Found: C, 66.4; H, 3.7; N, 6.2.

3-(4,4-Dimethyloxazolin-2-yl)-4-(2-methoxy-3-hydroxyphenyl)pyridine (17). Methionine (65.0 mg, 0.436 mmol) was added to compound **10** (0.1355 g, 0.434 mmol) in methanesulfonic acid (0.75 mL), and the mixture was heated at 85 °C for 90 h, poured into 1 M NaOH, and brought to pH 8 with 5 M H_3PO_4. Extraction with chloroform which was dried, evaporated, and chromatographed (MPLC, 1% CH_3OH, 0.05% TEA/$CHCl_3$) afforded 36 mg (27%) of recovered **10**, 14 mg (14%) of **15**, and 35.0 mg (27%) **17**: mp 178–180 °C; ^{1}H NMR δ 9.04 (s, 1 H), 8.71 (d, 1 H, J = 5.0 Hz), 7.38 (d, 1 H, J = 5.0 Hz), 7.03 (m, 2 H), 6.78 (dd, 1 H, J = 2.3, 6.9 Hz), 3.86 (s, 2 H), 3.41 (s, 3 H), 1.30 (s, 6 H); mass spectrum, m/z (relative intensity) 298 (0.24), 281 (3.2), 267 (100), 213 (23); exact mass calcd for $C_{17}H_{18}N_2O_3$ m/z 298.1318, found m/z 298.1318.

1-Methoxy-2-(methoxymethoxy)benzene (19). Guaiacol (27.0 g, 0.217 mol) was dissolved in a solution of sodium (4.88 g, 0.217 mol) in methanol (250 mL), the solvent was evaporated, and the residue was dried at 80 °C (0.2 mm) for 12 h. The sodium salt was suspended in THF (200 mL) and cooled to −23 °C, and chloromethyl methyl ether (17.0 mL, 0.224 mol) was added over 90 min. The suspension was stirred for 1 h and then at room temperature for 1 h, concentrated, and diluted with ether which was washed with 1 M NaOH, dried, and evaporated. The residue was distilled to afford 28.8 g (79%) of a colorless liquid: bp 123–125 °C (12 mm); ^{1}H NMR δ 7.16 (m, 1 H), 6.90 (m, 3 H), 5.22 (s, 2 H), 3.87 (s, 3 H), 3.51 (s, 3 H).

3-(4,4-Dimethyl-2-oxazolinyl)-4-[2-(methoxymethoxy)-3-methoxyphenyl]-1,4-dihydropyridine (20). *n*-Butyllithium (9.30 mL, 13.9 mmol, 1.49 M in hexane) was added to **19** (2.259 g, 13.4 mmol) in THF (35 mL) at −23 °C. The mixture was stirred for 45 min and then cooled to −45 °C before **3**[11] (2.846 g, 16.15 mmol) in THF (20 mL) was added over 50 min. The reaction was stirred for 1 h, warmed to 0 °C, stirred for 1 h, and quenched with water (25 mL) and saturated NaCl solution (25 mL). Extraction with ether (1 × 50 mL) followed by chloroform (3 × 50 mL) afforded 6.142 g of an oily yellow solid which was recrystallized from benzene/hexane to produce 2.147 g (46%) of **20** as pale yellow prisims: mp 167–176 °C; ^{1}H NMR δ 7.22 (dd, 1 H, J = 1.1, 5.5 Hz), 7.06 (dd, 1 H, J = 7.8, 7.9 Hz), 6.96 (dd, 1 H, J = 1.8, 7.9 Hz), 6.72 (dd, 1 H, J = 1.8, 7.8 Hz), 5.90 (dd, 1 H, J = 4.3, 7.7 Hz), 5.68 (m, 1 H), 5.24 (d, 1 H, J = 5.2 Hz), 5.21 (d, 1 H, J = 5.2 Hz), 5.03 (d, 1 H, J = 4.6 Hz), 4.88 (ddd, 1 H, J = 1.5, 4.6, 7.7 Hz), 3.82 (s, 3 H), 3.78 (d, 1 H, J = 7.8 Hz), 3.71 (d, 1 H, J = 7.8 Hz), 3.66 (s, 3 H), 1.15 (s, 3 H), 1.02 (s, 3 H); UV λ_{max} 275 nm (ϵ 7590); mass spectrum, m/z (relative intensity) 344 (44), 300 (20), 299 (100), 228 (25), 177 (42); exact mass calcd for $C_{19}H_{24}N_2O_4$ m/z 344.1736, found m/z 344.1727.

3-(4,4-Dimethyl-2-oxazolinyl)-4-[2-(methoxymethoxy)-3-methoxyphenyl]pyridine (22). *o*-Chloranil (6.00 g, 24.4 mmol) was added to a toluene (150 mL) suspension of crude dihydropyridine **20** (10.95 g, 20 mmol). The mixture was stirred 18 h and poured onto a dry, alumina (100 g, activity 3) column. Elution with ethyl acetate afforded 5.62 g (80%) of **22** as a white solid: mp 79–81 °C; bp 170 °C (0.02 mm); ^{1}H NMR δ 9.05 (d, 1 H, J = 0.5 Hz), 8.68 (d, 1 H, J = 5.0 Hz), 7.35 (dd, 1 H, J = 0.5, 5.0 Hz), 7.14 (dd, 1 H, J = 7.6, 8.1), 6.98 (dd, 1 H, J = 1.5, 8.1 Hz), 6.89 (dd, 1 H, J = 1.5, 7.6 Hz), 4.84 (s, 2 H), 3.88 (s, 3 H), 3.87 (s, 2 H), 2.94 (s, 3 H), 1.30 (s, 6 H); ^{13}C NMR δ 161.4, 152.3, 150.8, 150.3, 146.2, 143.2, 133.8, 125.5, 125.0, 124.3, 121.6, 112.8, 98.4, 79.6, 67.6, 56.7, 56.0, 27.1; UV λ_{max} 255 nm (ϵ 9330). Anal. Calcd for $C_{19}H_{22}N_2O_4$: C, 66.6; H, 6.5; N, 8.2. Found: C, 66.6; H, 6.5; N, 8.2.

Isolated as a forefraction was 0.119 g of **2-[2-(methoxymethoxy)-3-methoxyphenyl]-3-(4,4-dimethoxy-2-oxazolinyl)-pyridine (23)**: mp 111–113 °C; bp 160–170 °C (0.03 mm); ^{1}H NMR δ 8.76 (dd, 1 H, J = 1.8, 4.8 Hz), 8.18 (dd, 1 H, J = 1.8, 7.8 Hz), 7.31 (dd, 1 H, J = 4.8, 7.8 Hz), 7.17 (m, 2 H), 6.98 (dd, 1 H, J = 3.8, 5.9 Hz), 4.82 (s, 2 H), 3.91 (s, 2 H), 3.86 (s, 3 H), 2.94 (s, 3 H), 1.29 (s, 6 H); ^{13}C NMR δ 162.9, 156.3, 152.6, 151.3, 144.1, 138.1, 136.3, 126.3, 124.9, 123.0, 122.2, 113.5, 99.1, 80.3, 68.0, 57.2, 56.6, 28.6; UV λ_{max} 249 nm (ϵ 9770). Anal. Calcd for $C_{19}H_{22}N_2O_4 \cdot {}^1/_2H_2O$: C, 65.8; H, 6.3; N, 8.1. Found: C, 65.8; H, 6.4; N, 8.0.

7-Methoxy[1]benzopyrano[3,4-*c*]pyridin-5(2*H*)-one (15). *o*-Chloranil (3.635 g, 14.78 mmol) was added to a toluene (100 mL) suspension of crude **20** (6.142 g, 11–12 mmol). The mixture was stirred for 12 h, evaporated, dissolved in chloroform, and washed with 1 M NaOH (3 × 50 mL). The combined aqueous phases were filtered and extracted with chloroform (3 × 30 mL), the combined organic phases were evaporated, and the residue was dissolved in either (100 mL) and extracted into 1 M HCl (4 × 30 mL). The acid solution was refluxed for 6 h, made alkaline with K_2CO_3, and extracted with chloroform. Evaporation of the chloroform and chromatography (gravity column, 50/50 ethyl acetate/chloroform) of the residue afforded 2.147 g (70% from **19**) of **15** as a white solid: mp 198–200 °C; ^{1}H NMR δ 9.56 (d, 1 H, J = 0.7 Hz), 8.95 (d, 1 H, J = 5.6 Hz), 7.90 (dd, 1 H, J = 0.7, 5.6 Hz), 7.62 (dd, 1 H, J = 1.3, 8.1 Hz), 7.32 (dd, 1 H, J = 8.1, 8.2 Hz), 7.15 (dd, 1 H, J = 1.3, 8.2 Hz), 3.99 (s, 3 H); ^{13}C NMR δ 159.4, 154.3, 153.1, 148.2, 142.5, 141.8, 124.9, 116.8, 116.5, 115.6, 114.7, 114.5, 56.4; UV λ_{max} 277 nm (ϵ 13 800). Anal. Calcd for $C_{13}H_9NO_3$: C, 68.7; H, 4.0; N, 6.2. Found: C, 68.7; H, 4.0; N, 6.2.

Also isolated as a forefraction was 0.113 g (3.7%) of **7-methoxy-5-oxo[1]benzopyrano[4,3-*b*]pyridine (18)**: mp 210–212 °C; ^{1}H NMR δ 9.02 (dd, 1 H, J = 1.8, 4.7 Hz), 8.63 (dd, 1 H, J

= 1.8, 8.0 Hz), 8.15 (dd, 1 H, J = 1.4, 8.0 Hz), 7.53 (dd, 1 H, J = 4.7, 8.0 Hz), 7.33 (dd, 1 H, J = 8.0, 8.1 Hz), 7.14 (dd, 1 H, J = 1.4, 8.1 Hz), 4.00 (s, 3 H); ^{13}C NMR δ 160.7, 155.8, 152.2, 147.8, 138.3, 124.8, 124.0, 120,2, 117.6, 116.0, 114.1, 56.5; UV λ_{max} 273 nm (ε 17 400). Anal. Calcd for $C_{13}H_9NO_3$: C, 68.7; H, 4.0; N, 6.2. Found: C, 68.6; H, 3.9; N, 6.1.

3-[(3-Ethyl-3-pentoxy)carbonyl]-4-[2-[(ethoxycarbonyl)-methoxy]-3-methoxyphenyl]pyridine (24f). Lactone **15** (2.971 g, 13.1 mmol) was dried at 75 °C (0.05 mm) for 12 h, suspended in DMF (40 mL) and cooled to −65 °C (CO_2/$CHCl_3$). Potassium 3-ethyl-3-pentoxide[21] (2.270 g, 14.7 mmol) in DMF (18 mL) was added over 30 min, the mixture was stirred for 30 min, and ethyl bromoacetate (1.6 mL, 14.4 mmol) in DMF (12 mL) was added over 30 min. After being stirred for 30 min, the mixture was warmed to room temperature, and stirred for 1 h, and the solvent was removed by bulb to bulb distillation (50 °C pot, −78 °C receiver). The residue was partitioned between ether and saturated $NaHCO_3$ solution, the ether was dried and evaporated, and the residue was chromatographed (MPLC, 75/25 ether/isooctane) to afford 5.399 g (96%) of **24f** as a pale yellow oil: ^{1}H NMR δ 9.08 (s, 1 H), 8.67 (d, 1 H, J = 5.1 Hz), 7.30 (dd, 1 H, J = 0.5, 5.1 Hz), 7.10 (dd, 1 H, J = 7.6, 8.3 Hz), 6.96 (dd, 1 H, J = 1.6, 8.3 Hz), 6.76 (dd, 1 H, J = 1.6, 7.6 Hz), 4.44 (s, 2 H), 4.07 (q, 2 H, J = 7.1 Hz), 3.87 (s, 3 H), 1.79 (q, 6 H, J = 7.5 Hz), 1.16 (t, 3 H, J = 7.1 Hz), 0.76 (t, 9 H, J = 7.5 Hz); ^{13}C NMR δ 169.1, 164.9, 151.9, 151.0, 150.8, 146.8, 144.1, 133.3, 128.4, 126.1, 124.1, 121.6, 112.9, 90.5, 69.7, 60.8, 56.0, 26.8, 14.2, 7.7; UV λ_{max} 261 nm (ε 5890). Anal. Calcd for $C_{24}H_{31}NO_6$: C, 67.1; H, 7.3; N, 3.3. Found: C, 66.9; H, 7.3; N, 3.3.

1-Methyl-3-[(3-ethyl-3-pentoxy)carbonyl]-4-[2-[(ethoxycarbonyl)methoxy]-3-methoxyphenyl]pyridinium Iodide (25f). To **24f** (3.733 g, 8.7 mmol), dried at 75 °C (0.05 mm) for 12 h, was added iodomethane (25 mL). After the solution was stirred at room temperature 6 h, the excess iodomethane was evaporated to yield 4.98 g (100%) of **25f** as a yellow foam: ^{1}H NMR δ 9.72 (dd, 1 H, J = 1.4, 6.3 Hz), 9.14 (d, 1 H, J = 1.4 Hz), 8.05 (d, 1 H, J = 6.3 Hz), 7.21 (dd, 1 H, J = 7.6, 7.7 Hz), 7.10 (dd, 1 H, J = 1.6, 7.7 Hz), 6.92 (dd, 1 H, J = 1.6, 7.6 Hz), 4.82 (s, 3 H), 4.58 (s, 2 H), 4.02 (q, 2 H, J = 7.1 Hz), 3.91 (s, 3 H), 1.77 (q, 6 H, J = 7.5 Hz), 1.17 (t, 3 H, J = 7.1 Hz), 0.72 (t, 9 H, J = 7.5 Hz); ^{13}C NMR δ 168.5, 163.4, 155.7, 151.2, 146.1, 144.7, 143.4, 132.8, 130.8, 130.0, 124.7, 120.5, 114.8, 93.7, 68.9, 60.7, 56.0, 49.5, 26.6, 14.0, 7.6; UV λ_{max} 305 nm (ε 6170).

Spiro[2-(ethoxycarbonyl)-7-methoxybenzofuran-3-(2H),4'-1'-methyl-3'-[(3-ethyl-3-pentoxy)carbonyl]-1',4'-dihydropyridine] (26f). Pyridinium salt **25f** (from 3.733 g, 8.7 mmol of **24f**) was treated with sodium ethoxide (11.3 mmol) in ethanol (70 mL), heated to reflux for 1 h, and then poured into saturated $NaHCO_3$ (100 mL) and water (100 mL). The mixture was extracted with ether (3 × 70 mL) which was dried and evaporated to give 3.725 g of crude **26f** as a yellow oil. Chromatography (MPLC, 50/50 ether/isooctane) of 0.824 g of the oil afforded 0.607 g (71%) of a white solid: mp 108–110 °C; ^{1}H NMR δ 7.34 (d, 1 H, J = 1.8 Hz), 6.84 (dd, 1 H, J = 7.2, 8.1 Hz), 6.71 (m, 2 H), 5.79 (dd, 1 H, J = 1.8, 7.9 Hz), 5.32 (s, 1 H), 4.62 (d, 1 H, J = 7.9 Hz), 4.23 (m, 2 H), 3.87 (s, 3 H), 3.09 (s, 3 H), 1.60 (m, 6 H), 1.25 (t, 3 H, J = 7.1 Hz), 0.58 (t, 9 H, J = 7.5 Hz); ^{13}C NMR δ 169.4, 166.5, 145.2, 144.0, 142.0, 137.3, 126.8, 121.9, 117.0, 111.3, 106.5, 100.0, 92.2, 88.6, 60.7, 56.0, 51.6, 41.0, 26.3, 14.4, 7.6; UV λ_{max} 347 nm (ε 5810), 284 (1600). Anal. Calcd for $C_{25}H_{33}NO_6$: C, 67.7; H, 7.5; N, 3.2. Found: C, 67.8; H, 7.6; N, 3.2.

Spiro[2-(ethoxycarbonyl)-7-methoxybenzofuran-3-(2H),4'-1'-methyl-3'-[(3-ethyl-3-pentoxy)carbonyl]-1',4',5',6'-tetrahydropyridine] (28). The crude dihydropyridine **26f** (488 mg, 1.0 mmol) in ethanol (20 mL) was treated with 10% palladium on carbon (200 mg) and hydrogenated at 50–55 psi for 48 h. The mixture was filtered, evaporated, and chromatographed (MPLC, 60/40 isooctane/ether) to afford 265 mg (59%) of the α isomer of **28** followed by 85 mg (19%) of the β isomer.[17]

α isomer of 28: bp 120 °C (0.002 mm); ^{1}H NMR δ 7.64 (s, 1 H), 6.80 (dd, 1 H, J = 7.2, 8.1 Hz), 6.72 (dd, 1 H, J = 1.4, 8.1 Hz), 6.54 (dd, 1 H, J = 1.4, 7.2 Hz), 5.67 (s, 1 H), 4.25 (m, 2 H), 3.87 (s, 3 H), 3.04 (m, 1 H), 3.01 (s, 3 H), 2.85 (m, 1 H), 2.12 (ddd, 1 H, J = 3.9, 5.4, 14.1 Hz), 1.78 (m, 1 H), 1.54 (m, 6 H), 1.28 (t, 3 H, J = 7.1 Hz), 0.61 (t, 9 H, J = 7.5 Hz); ^{13}C NMR δ 169.6, 166.5, 149.3, 146.0, 144.4, 137.1, 121.6, 114.9, 111.2, 95.6, 87.3, 60.9, 56.0, 47.7, 44.6, 42.9, 32.5, 26.7, 14.3, 7.7; UV λ_{max} 290 nm (ε 16 600). Anal. Calcd for $C_{25}H_{35}NO_5$: C, 67.4; H, 7.9; N, 3.1. Found: C, 67.6; N, 8.0; N, 3.2.

β isomer of 28: ^{1}H NMR δ 7.48 (s, 1 H), 6.79 (dd, 1 H, J = 7.2, 8.1 Hz), 6.72 (dd, 1 H, J = 1.4, 8.1 Hz), 6.53 (dd, 1 H, J = 1.4, 7.2 Hz), 4.64 (s, 1 H), 4.12 (m, 2 H), 3.88 (s, 3 H), 3.42 (m, 1 H), 3.12 (m, 1 H), 3.04 (s, 3 H), 2.02 (m, 2 H), 1.55 (m, 6 H), 1.24 (t, 3 H, J = 7.2 Hz), 0.67 (t, 9 H, J = 7.5 Hz); ^{13}C NMR δ 168.9, 166.1, 148.3, 146.9, 144.4, 134.6, 121.5, 115.0, 111.0, 95.2, 91.6, 86.7, 61.1, 55.8, 48.8, 44.3, 43.0, 38.6, 27.1, 14.2, 7.9.

Spiro[2-(ethoxycarbonyl)-7-methoxybenzofuran-3-(2H),4'-1'-methyl-3'-[(3-ethyl-3-pentoxy)carbonyl]piperidine] (29). Tetrahydropyridine **28** (81.5 mg, 0.18 mmol) in ethhanol (6 mL) was treated with a trace of bromocresol green and NaCNBH$_3$ (41.6 mg, 0.66 mmol), The solution immediately turned blue, and 2 M HCl–ethanol was added to the point of just restoring the yellow color. The reaction was stirred for 4 h with acid added as necessary. A second portion of NaCNBH$_3$ (25 mg, 0.40 mmol) was added, and the suspension was stirred for 8 h, concentrated, diluted with 1 M H_3PO_4 (20 mL, **Caution**: HCN evolution), and stirred for 1 h at which point gas evolution had ceased. The mixture was washed with ether, made alkaline with K_2CO_3, and extrcted with chloroform which on drying and evaporation yielded 79.0 mg (96%) of **29** as a palle yellow oil: bp 110–115 °C (0.002 mm); ^{1}H NMR δ 7.12 (dd, 1 H, J = 2.9, 6.8 Hz), 6.80 (m, 2 H), 5.49 (maj), 5.58 (diastereomeric singlets, 1 H), 4.28 (m, 2 H), 3.86 (s, 3 H), 2.39 (maj), 2.34 (diastereomeric singlets, 3 H), 1.8–3.2 (m, 7 H), 1.68 (m, 6 H), 1.30 (m, 3 H), 0.60 (t, 9 H, J = 7.5 Hz); UV λ_{max} 278 nm (ε 2100). Anal. Calcd for $C_{25}H_{37}NO_6$: C, 67.1; H, 8.3; N, 3.1. Found: C, 67.2; H, 8.4; N, 3.2.

Ring Closure and Reduction Sequence. Piperidine diester **29** was prepared in 75% yield from 4-arylnicotinate **24f** without any intermediate purifications.

Spiro[2-(ethoxycarbonyl)-7-methoxybenzofuran-3-(2H),4'-1'-methylpiperidine-3'-carboxylic acid] (30). A solution of piperidine **29** (0.543 g, 1.21 mmol) in *n*-propanol (9 mL), water (9 mL), and acetic acid (2 mL)[22] was heated to reflux for 6 h, evaporated and dried at 100 °C (0.05 mm) for 12 h to afford **30** as its acetic acid salt: ^{1}H NMr δ 6.90 (m, 1 H), 6.75 (m, 2 H), 5.62 (maj), 5.49 (diastereomeric singlets, 1 H), 4.20 (m, 2 H), 3.79 (s, 3 H), 2.8–3.4 (m, 5 H), 2.44 (s, 3 H), 1.9–2.1 (m, 2 H), 1.93 (s, 3 H), 1.27 (t, 3 H, J = 7.1 Hz).

Spiro[2-(ethoxycarbonyl)-7-methoxybenzofuran-3-(2H),4'-1'-methyl-3'-methylene-2'-piperidinone] (31). (A) From Acid Ester 30. A solution of **30** (from 0.543 g, 1.21 mmol **29**) in acetic anhydride (15 mL) was heated to reflux for 24 h and evaporated. The residue was dissolved in $CHCl_3$, washed with saturated $NaHCO_3$ solution, dried, and evaporated. Chromatography (MPLC, ether) afforded 0.249 g (62%) of a colorless oil: bp 140–150 °C (0.04 mm); ^{1}H NMR δ 6.91 (dd, 1 H, J = 7.2, 8.2 Hz), 6.84 (dd, 1 H, J = 1.4, 8.2 Hz), 6.59 (dd, 1 H, J = 1.4, 7.2 Hz), 6.59 (d, 1 H, J = 0.5 Hz), 5.34 (d, 1 H, J = 0.5 Hz), 5.19 (s, 1 H), 4.25 (m, 2 H), 3.80 (s, 3 H), 3.42 (m, 2 H), 3.10 (s, 3 H), 2.18 (m, 1 H), 2.05 (m, 1 H), 1.28 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 168.3, 163.1, 146.5, 144.9, 140.5, 132.6, 124.7, 122.7, 115.4, 112.5, 88.5, 61.6, 56.1, 53.0, 45.5, 35.5, 28.8, 14.2; UV λ_{max} 275 nm (ε 2900). Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.2; H, 6.4; N, 4.2. Found: C, 64.9; H, 6.4; N, 4.2.

(B) Equilibration of 31. Methylene lactam ester **31** (85.0 mg, 0.26 mmol) was treated with NaOEt (0.10 mmol) in ethhanol (10 mL) and heated to reflux for 24 h. The mixture was poured into saturated $NaHCO_3$ solution (10 mL), and water (10 mL) was added followed by extraction with chloroform, which was dried and evaporated. Chromatography (MPLC, 75/25 ether/isooctane) afforded 3.5 mg (4%) of recovered α isomer followed by 58.5 mg (69%) of the β isomer: ^{1}H NMR δ 6.92 (dd, 1 H, J = 7.2, 8.1 Hz), 6.83 (dd, 1 H, J = 1.3, 8.1 Hz), 6.63 (dd, 1 H, J = 1.3, 7.4 Hz), 6.56 (d, 1 H, J = 1.4 Hz), 5.22 (d, 1 H, J = 1.4 Hz), 5.14 (s, 1 H), 4.04 (m, 2 H), 3.92 (s, 3 H), 3.36 (m, 2 H), 3.09 (s, 3H), 2.35 (m, 1 H), 2.06 (m, 1 H), 1.19 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 168.3,

(21) Prepared by the reaction of potassium with excess triethylcarbinol at reflux, distillation of the excess alcohol, and sublimation of the residue.

(22) Johansen, J. E.; Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 4914.

162.7, 142.5, 144.7, 139.0, 132.0, 127.2, 122.6, 116.0, 112.3, 87.6, 61.6, 56.1, 55.4, 45.5, 35.6, 35.2, 14.0. Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.2; H, 6.4; N, 4.2. Found: C, 65.1; H, 6.6; N, 4.2.

(C) From Diacid 32. A solution of **30** (from 183 mg, 0.41 mmol of **29**) in methanol (5 mL) was treated with potassium hydroxide (86 mg, 1.3 mmol) in water (5 mL) and heated to reflux for 3 h. Acetic acid (0.10 mL) was added, the solvent was evaporated, and the residue was dried at 90 °C (0.05 mm) for 18 h. The crude diacid was heated at reflux in acetic anhydride (10 mL) for 24 h and evaporated to a white solid. This residue was dissolved in ethanol, treated with boron trifluoride etherate (1.0 mL, 8.1 mmol), heated at reflux for 24 h, and poured into saturated $NaHCO_3$ solution. Extraction with chloroform, drying, solvent evaporation, and chromatography (MPLC, 75/25 ether/isooctane) afforded 12.5 mg (9%) of the α isomer followed by 81.0 mg (60%) of the β isomer.

Spiro[7-methoxybenzofuran-2-carboxylic acid-3(2*H*),4'-1'-methyl-3'-methylene-2'-piperidinone] (2). Ethyl ester **31** (84.0 mg, 0.254 mmol) in methanol (5 mL) at 0 °C was treated with 1 M aqueous KOH (5 mL). The mixture was stirred for 1.25 h, acidified with 1 M HCl (10 mL), and extracted with $CHCl_3$ which was dried and evaporated to afford 77.0 mg (100%) of a white solid: mp 185-187 °C (lit.[3] mp 184-186 °C); ^1H NMR δ 6.85 (dd, 1 H, J = 7.8 Hz), 6.72 (d, 1 H, J = 7 Hz), 6.57 (d, 1 H, J = 8 Hz), 6.55 (s, 1 H), 5.40 (s, 1 H), 5.08 (s, 1 H), 3.71 (s, 3 H), 2.98 (s, 3 H), 3.0-3.4 (m, 2 H), 1.8-2.2 (m, 2 H).

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Registry No. α-**2**, 87903-06-8; β-**2**, 87903-24-0; **3**, 68981-86-2; **4**, 68981-78-2; **5**, 87903-19-3; **7**, 87902-89-4; **8**, 87903-21-7; **9**, 87903-20-6; **10**, 87902-86-1; **11**, 87902-87-2; **12**, 87902-88-3; **15**, 87308-11-0; **16**, 87902-90-7; **17**, 87902-91-8; **18**, 87902-95-2; **19**, 73220-26-5; **20**, 87902-92-9; **22**, 87902-93-0; **23**, 87902-94-1; **24a**, 87903-07-9; **24b**, 87903-08-0; **24c**, 87921-95-7; **24d**, 87903-09-1; **24e**, 87903-10-4; **24f**, 87902-96-3; **25f**, 87902-97-4; **26a**, 87921-96-8; **26b**, 87903-11-5; **26c**, 87903-12-6; **26d**, 87903-13-7; **26e**, 87903-14-8; α-**26f**, 87902-98-5; β-**26f**, 87903-22-8; **27a**, 87903-15-9; **27b**, 87903-16-0; **27c**, 87903-17-1; **27d**, 87903-18-2; α-**28**, 87902-99-6; β-**28**, 87903-00-2; **29**, 87903-01-3; **30**, 87902-02-4; **30** acetate, 87903-03-5; **30** diacid, 87903-05-7; α-**31**, 87903-23-9; β-**31**, 87903-04-6; veratrole, 91-16-7; guaiacol, 90-05-1; chloromethyl methyl ether, 107-30-2; ethyl bromoacetate, 105-36-2; codeine, 76-57-3.

The Diverse Carbenic and Cationic Chemistry of 3-Diazo-2,5-diphenylpyrrole

M. Nagarajan and H. Shechter*

Chemistry Department, The Ohio State University, Columbus, Ohio 43210

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3-Diazo-2,5-diphenylpyrrole (**1**) thermolyzes and photolyzes to 2,5-diphenyl-3*H*-pyrrolylidene (**3**), which inserts into methylene hydrogen of cyclohexane and methyne hydrogen of cumene. Hydrogen abstraction to give 2,5-diphenylpyrrole (**7**) occurs competitively in these systems. Carbene **3** reacts with cyclohexene, allylbenzene, and 2,3-dimethyl-2-butene to give 3-(allylically substituted)-2,5-diphenylpyrroles (**15**, **20**, **21**, and **29**) as the only products of olefin incorporation along with **7**. The initial position of the double bond in the olefin may be altered in the overall insertion process, and cyclopropanes are not isolable. The apparent behavior of **3** with saturated and olefinic hydrocarbons is as singlet **8s** and triplet **9t**. Reactions of **3** with anisole (**31a**) and with toluene (**31b**), benzenes substituted by electron-donor groups, result in selective ortho and/or para substitution to give 2,5-diphenyl-3-(substituted-phenyl)pyrroles (**38a**, **35**, and **38b**) and in hydrogen abstraction to **7**. Insertion into the methyl groups and hydrogen abstraction also occur in reactions of **3** with **31b**, yielding 3-benzyl-2,5-diphenylpyrrole (**39**) and 1,2-diphenylethane (**40**). Benzene (**42a**), however, reacts thermally or photolytically with **1** to form 1,3-diphenyl-2*H*-cycloocta[*c*]pyrrole (**46a**), a member of a new heterocyclic system. Ring expansions to 4-, 5-, and 6-cyano-1,3-diphenyl-2*H*-cycloocta[*c*]pyrroles (**46b**, **46b'**, and **46b''**) and 4-, 5-, and 6-nitro-1,3-diphenyl-2*H*-cycloocta[*c*]pyrroles (**46c**, **46c'**, and **46c''**) are the principal reactions of **3** with benzonitrile (**42b**) and nitrobenzene (**42c**). 3-(*m*-Nitrophenyl)-2,5-diphenylpyrrole (**47b**) is also formed from **1** and **42c** at 170 °C. Thermolysis and photolysis of **1** to effect substitution and ring expansion of benzenes may involve electrophilic attack of **8s** to form spiropyrrolonorcaradienes (**32**). Directed heterolytic ring opening of **32** and (1,5 sigmatropic) rearrangements of hydrogen will rationalize the selective ortho and/or para substitution processes. Cycloocta[*c*]pyrroles may arise from (electrocyclic) isomerization of **32** to spirocycloheptatrienes **44**, (1,5 sigmatropic) rearrangement involving ring expansion to **45**, and then hydrogen migration. Triplet photosensitization of **1** in **42a** and **42b** leads to 2,3,5-triphenylpyrrole (**47a**) and 3-(*o*-cyanophenyl)-2,5-diphenylpyrrole (**47c**), products of aromatic substitution rather than ring expansion. Such photolytic processes may involve generation and then addition of **9t** to **42a** and **42b**, spin inversion of the triplet to singlet diradical intermediates, and successive hydrogen migrations. Aniline (**59a**), *N*-methylaniline (**59b**), and *N*,*N*-dimethylaniline are nucleophiles in that they are pyrrylated on nitrogen by **1** at 180 °C. Primary and secondary alcohols and **1** undergo oxidation/reduction to carbonyls and **7**; conversion to 3-alkoxy-2,5-diphenylpyrroles is minor except in the presence of external acid. 2,5-Diphenyl-3-pyrrolediazonium salts (**2**) effect 2,5-diphenylpyrrylation of aromatics upon thermolysis and photolysis. The orientation, utility, and mechanisms of reactions of **2** with benzenes are significantly different than for thermolysis, photolysis, and photosensitization of **1**.

Although diazopyrroles were first synthesized over 70 years ago,[1] very little is known about their chemistry. Photolysis of 3-diazo-2,4,5-triphenylpyrrole in benzene and in methanol produces 2,3,4,5-tetraphenylpyrrole and 2,3,5-triphenylpyrrole, respectively.[2] [3 + 2] Cycloaddition of 3-diazo-2,4,5-triphenylpyrrole with cyclooctyne and then 1,5-rearrangement gives 2,3-cyclooctano-4,5,7-triphenylpyrazolo[1,5-*c*]pyrimidine.[3] 3-Diazo-2,5-diphenylpyrrole

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